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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/435,257	PAUL A. CLEMONS	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-51 is/are pending in the application.

4a) Of the above claim(s) ~~19 and 38-50 is/~~are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18, 20-37, and 51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/8/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendment received December 12, 2003 has been entered. Claims 38 and 39 have been cancelled. Examiners answers are at the end of this office action.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 4-18, 20-28, 32-37 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 4-18, 22, 24, 27, 33 of copending Application No. 09/831,096.

Claims 1, 4-18, 22, 24, 27, 33 of the instant application are identical to claims 1, 4-18, 22, 24, 27, 33 of application 09/831,096.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

DETAILED ACTION

Applicant's arguments filed December 12, 2004 have been fully considered but they are not persuasive. The amendment has been entered. Claims 38 and 39 have been cancelled. Claims 1-19, 21-37 and 51 are pending. Applicant's response is addressed at the end of this office action where relevant given the new grounds of rejection.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 4-18, 20-28, 32-37 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 4-18, 22, 24, 27, 33 of copending Application No. 09/831,096.

Claims 1, 4-18, 20-28 and 32-37of the instant application are identical to claims 1, 4-18, 22, 24, 27, 33 of application 09/831,096.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 29-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-50 of copending Application No. 09/831,096. Although the conflicting claims are not identical, they are not patentably distinct from each other because the specific sequences claimed are contained within the full-length calcineurin A and B sequences claimed in '096.

Claims 1-3 are drawn to recombinant nucleic acid encoding a CAB domain comprising a portion of calcineurin A and calcineurin B wherein the CAB domain forms a tripartite complex with a FKBP ligand and a FKBP domain, and said recombinant nucleic acid wherein the calcineurin A portions is encoded by SEQ ID NO 33 and the calcineurin B portion is encoded by SEQ ID NO 35. Claims 29-31 are drawn to an isolated cell of human origin which comprises a host cell comprising a recombinant nucleic acid encoding portions of calcineurin A and B and a isolated cell of human origin which comprises a host cell comprising SEQ ID NO's 33 and 35. Claims 1-50 of application 09/831,096 are directed to a recombinant nucleic acid encoding a CAB domain, comprising a portion of calcineurin A and calcineurin B which wherein the CAB domain forms a complex with a FKBP ligand and a FKBP domain, cells, vector, fusion protein and non-human animals comprising said recombinant nucleic acid and methods for producing

and using said cells, vector, fusion protein and non-human animals which as defined by the specification contain SEQ ID NO's 33 and 35. Thus, present claims 1-3 and 29-31 are obvious over claims 1-50 of '096 because claims 1-50 of '096 are generic.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32, and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are interpreted to encompass a transgenic non-human animal when taken in light of the teachings of the specification (specification pg. 37 lines 13-32).

While the specification has provided guidance for transformation of a cell *in vitro* with the claimed nucleotide sequences, the instant specification has failed to provide any relevant teachings, guidance, or working examples that teach how to create a transgenic non-human animal that expresses a nucleotide sequence encoding a CAB domain, wherein expression of a CAB domain fusion protein results in an animal having a use in the art as a disease model or any type of model related to CAB [illegible]

purpose a transgenic animal containing cells comprising a nucleic acid encoding CAB, and none is apparent. Further, the specification does not disclose any particular disease associated with the overexpression of CAB. Also, it is noted, the claims merely require that the transgenic animal contain the cells but there is no requirement for expression much less expression to any result in any phenotype. It is not clear from the specification how a transgenic animal merely containing the cells would be useful.

As the specification fails to provide any relevant teachings or guidance with regard to the production of a transgenic animal as claimed, one skilled in the art would not be able to rely on the state of the transgenic art for an attempt to produce CAB domain transgenic animals that have a particular use in the art. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype, especially in the present case where no behavioral or physiological changes are associated with transgene expression. While the state of the art of transgenics is such that one skilled in the art would be able to produce transgenic animals comprising a transgene of interest, it is not predictable if the transgene could be expressed at a level and specificity sufficient to cause a particular phenotype that can be correlated to a specific use for the transgenic animal. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animals which exhibits a resulting phenotype. This observation is supported by Wall

(Theriogenology, 1996) who states that "our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior," See pg. 61, last paragraph). See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (pg. 75 col. 1, parag. 1 e.g., specific promoters, presence or absence of introns, etc). The claims as written do not require a particular promoter to direct expression of a nucleotide sequence encoding a CAB domain. In addition, the instant specification has failed to describe any promoter that could be used to direct expression of said nucleotide sequence in a particular cell type to produce a desired phenotype. As such guidance is lacking in the instant specification, the specification fails to feature any correlation between the expression of a CAB domain transgene in any host animal, and, thus, a specific resulting use of the transgenic animal.

Further, well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (pg. 256 Cameron (1997) Molec. Biol. 7, col. 1 -2, bridg. parag.). Factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (pg. 256. Cameron (1997), Molec. Biol. 7, lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (pg. 256 Cameron (1997), Molec. Biol. 7, lines 10-13). Further, Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the

observed phenotype (pg. 1426 Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, col. 1, parag. 1, lines 1-7). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to the pig, the other compatible with pig health (pg. 73 Niemann (1997) Transg. Res. 7, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combinations). This observation is specifically supposed by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs, however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pgs. 276-277, Subsection: Effect of Foreign GH on Growth). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another " (pg. 539, Summary). Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." (pg. 62, parag. 1). Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CPG methylation (pg. 549, col. 2, 3rd full paragraph). Given these art recognized unpredictabilities for obtaining transgenic expression, particularly when taken with the lack of guidance in the specification for the production of even one transgenic animal whose genome comprises a CAR d[illegible]

undue experimentation to obtain any one host animal comprising and expressing a CAB: domain transgene where the animal would have a use to the art at the time of filing Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of CAB transgenic animals, the lack of direction or guidance provided by the specification for the production of any transgenic animal expressing a transgene encoding a CAB domain for use, the absence of working examples for the demonstration or correlation to the production of a transgenic animal expressing a transgene encoding a CAB domain, in particular when the transgene comprises CAB coding sequences under the control of any promoters, and more particularly when the expression of the transgene must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to transgene behavior in transgenic animals of any species, and the breadth of the claim drawn to any animals it would have required undue experimentation without a predictable degree of success for one skilled in the art to make and/or use the claimed invention at the time of filing.

Claims 26-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell *in vitro* comprising a nucleotide sequence encoding a CAB domain and methods for producing genetically engineered host cells *in vitro*, does not reasonably provide enablement for is not enabling for a host cell *in vivo* comprising a CAB domain protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate

The claims are interpreted to encompass a somatic cell that has been transformed *in vivo* with one of the claimed nucleotide sequences. This embodiment reads on both in situ gene therapy and cell based or ex vivo gene therapy.

While the instant specification has provided guidance for transforming an isolated somatic cell *in vitro*, the instant specification however, has not provided any relevant teachings, guidance, or working examples that teach or otherwise correlate to transformation of a cell *in vivo* with one of the claimed CAB nucleotide sequences. The specification has failed to provide any guidance or working examples that correlate administration of said nucleotide sequence into a host with targeting of a particular disease or condition. In fact, nowhere in the specification is there any disclosure concerning diseases or conditions that could be remedied through the production of CAB. In addition, a search of the art does not provide any such diseases or conditions. Thus, the specification has failed to correlate expression of said CAB nucleotide sequence in a cell *in vivo* with any particular resulting effect that would have a use in the art as a disease or condition treatment. In light of the teachings of the instant specification is unclear what purpose expressing a CAB domain nucleotide sequence in the somatic cells of a host may serve other than to provide a therapeutic effect. One of skill would not be able to rely on the state of the art of in situ or ex vivo gene therapy to transform a somatic cell *in vivo* with a nucleotide sequence encoding a CAB domain protein for an effective treatment. The state of the art of gene therapy at the time the claimed invention was filed was unpredictable with respect to expression of a nucleotide sequence in a host cell *in vivo* sufficient to ameliorate any symptom associated with a disease, when a disease is ascribed. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

This is reflected by two reviews. Verma et al. teach that as of 1997, "there is still no single outcome that we can point to as a success story" (pg. 239, col. 1), The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (pg. 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (pg. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (pg. 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, pg. 30), it would require extensive research to understand the fundamental biology of the system. Thus in view of the lack of guidance and direction provided by the specification for gene therapy of any disease, it would have required one of skill in the ad undue experimentation to make and use the invention as claimed. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supposed by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pgs. 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg. 198, col. 1). Deonarain (1998, Expert. Opin. Ther. Pat., Vol. 8, pg. 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at

new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (pg. 65, parag. 1 under Conclusion section). Verma review's vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (pg. 240, sentence bridging cols. 2 and 3). Crystal (1995, Science, Vol. 270, pgs. 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (pg. 409).

Claims 30 and 31 are directed to host cells encapsulated ex vivo within a biocompatible material. While the instant specification has provided guidance for transforming an isolated somatic cell *in vitro*, the instant specification however, has not provided any relevant teachings, guidance, or working examples that teach or otherwise correlate to injecting transformed or encapsulated transformed cells into an animal that would be used as a therapeutic treatment. The specification has failed to provide any guidance or working examples that correlate administration of said transformed cells or encapsulated transformed cells into an animal with targeting of a particular disease or condition. Li taught at the time of filing taught that using encapsulated cells for therapeutic treatment in animals involves significant technical difficulties and formalities that must be considered (pg. 91 table 2). Li continues that "the most significant issue currently hampering microcapsule transplantation is the fibrotic reaction to the membrane leading to cell death" (pg. 95 col. 2 parag. 2 lines 2-5) and that "a other

continues to be the significant microcapsule volumes required for therapeutic dosage of islets (an estimated several hundred thousand beads); applications requiring smaller cell volumes such as CNS disorders are not appropriate implant locations since microcapsules may block CSF drainage in the lateral ventricles of the brain" (pg. 95 col. 2 parag. 2 lines 7-14).

Therefore, in view of the lack of direction or guidance provided by the instant specification for any diseases or conditions that could treated by production of CAB, the quantity of experimentation necessary to determine the parameters listed above for producing a cell transformed *in vivo* or an ex vivo encapsulated cell transformed with a claimed nucleotide sequence that would provide a useful treatment, the absence of working examples the demonstrate or otherwise correlate to transformation of a somatic cell *in vivo* with effective expression of the nucleic acid to alleviate any disease symptom, and the unpredictability of the art of gene therapy or ex vivo gene therapy with respect to obtaining any effect on any symptom of any disease or condition, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 20-21, 26, 34, and 36 are rejected under 35 U.S.C. 1O2(b) as being anticipated by Mondragon et al. (Biochemistry, 1997, 36: 4934-4942). Mondragon et al teach an artificial

operon comprising recombinant nucleic acid encoding both human calcineurin A and calcineurin B subunits packaged into a pET15b expression vector and transformed into *E. coli*. (pg. 4937 col. 2 parag. 3 lines 1-6 and fig. 2). The peptide sequence of Mondragon contains SEQ ID NO: 33 and 35. Further, the recombinant nucleic acid of Mondragon inherently encodes a CAB domain that forms a tripartite complex with an FKBP/CAB ligand. Mondragon continues to teach that mutations to amino acid residues, up to 10, in the active site resulted in limited structural disturbance to the structure of calcineurin compared to wild-type calcineurin (pg. 4939 col. 2 lines 3-8 and table 2). Further, the nucleic acid construct of Mondragon contains a poly-His tag, which is a signaling domain (page 4939, col. 2, parag, 2, lines 6-10). Mondragon et al. continue to teach that recombinantly produced calcineurin formed a complex with FKBP-FK506 in a dose dependent manner (pg. 4939 col. 1 parag. 2 lines 1-10 and fig. 5) and bound similarly to wild-type calcineurin (pg. 4939 col. 2 lines 3-7 and table 2). Thus, the teachings of Mondragon et al. anticipate claims 1-6, 11-12, 20-21, 26, 34, and 36 of the instant application.

Applicants have argued that cells comprising the recombinant nucleic acids of the present invention are enabled for the production of transgenic animals (pgs. 8-9 of the response filed 12/23/03). Applicants direct attention to their disclosure of a variety of uses for cells expressing the constructs comprising the claimed recombinant nucleic acid, further methods for expressing the subject constructs in cells, working examples demonstrating methods of expressing the constructs of the present invention in cells. Applicants contend that working examples demonstrate that the subject constructs can be expressed in cells, and further that the genetically engineered cells express functional proteins that are regulatable. However, applicant has failed to

address transgenic animals produced from the claimed cells comprising a recombinant nucleic acid of the present invention. Applicants do not disclose any related phenotype in a transgenic animal associated with the overexpression, reduction or removal of a recombinant nucleic acid encoding a CAB domain, or what the use of such a transgenic animal would be. Further, no disease has been disclosed that has been associated with a decrease or increase in a recombinant nucleic acid encoding a CAB domain. Thus, the purpose of in vivo or ex vivo administration of the nucleic acid molecules claimed is not enabled for therapeutic purposes. One skilled in the art at the time of filing would not find an enabled use for a transgenic animal that has a phenotype of normal i.e. no symptoms of any kind associated with any known disease or disorder, nor for a method of treatment using the claimed recombinant nucleic acid molecules. Therefore, applicant's arguments are not persuasive.

Claims 7-18, 22-25, 27-33, 35, 37 and 51 are free of the prior art at the time of filing.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari, Ph.D. whose telephone number is 571-272-3108. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1638

February 22, 2005